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Cobalt-Catalyzed α-Methoxymethylation and Aminomethylation of Ketones with Methanol as a C1 Source

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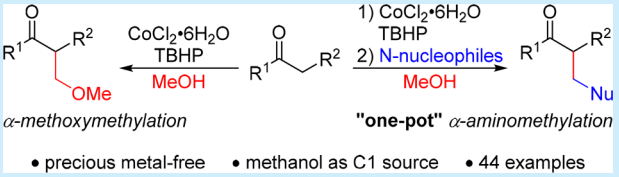
Supporting Information

ABSTRACT: Using methanol as a sustainable C1 source, cobalt-catalyzed α-methoxymethylation and α-aminomethylation of ketones have been developed. With cheap $CoCl_2·6H_2O$ as catalyst and TBHP as oxidant, the methoxymethylated products were obtained within a short reaction time in up to 91% yield. Based on the observed reversibility of methoxy adduct to enone, the α-aminomethylation of ketones was then achieved by a one-pot methylenation/aza-Michael addition sequence. In addition, an easy way to convert α-methoxymethyl ketones to α-aminomethyl ketones has been discovered.



C−H Bond functionalization represents an atom- and step-economic approach to construct valuable complex organic molecules in modern organic synthesis.[1] Compared to C(sp)−H and C(sp^2)−H bonds, C(sp^3)−H bond functionalization is more challenging due to its relatively low reactivity.[2] Recently, methanol has emerged as a "green" and "renewable" C1 source and has been used in diverse transformations.[3] A notable example is α-C(sp^3)−H methylation of ketones with methanol under the catalysis of Rh,[4] Ir,[5] Ru,[6] Co,[7] or Fe[8] by means of the borrowing hydrogen strategy.[9] In addition, sodium iodide catalyzed methoxylation[10] and visible-light photocatalytic hydroxymethylation[11] of ketones have also been realized. However, methoxymethylation of ketones with methanol has rarely been reported, with only one example known from Donohoe and co-workers.[5a] In their study, the methoxymethylated product was obtained by an iridium-catalyzed one-pot process in the presence of a phosphine ligand (Scheme 1a). As for aminomethylation using methanol as the C1 source, the aminomethylation of aromatic alcohols has been reported with Ru or Mn catalyst,[12] but the aminomethylation of ketone has not been achieved.

Our goal was to seek a more economic method to achieve α-C(sp^3)−H functionalization of ketones using methanol as a sustainable C1 building block. In recent years, the inexpensive, earth abundant first-row transition metal catalysts have shown wide application prospects in organic reactions.[13] Among them, cobalt is attractive because of its biocompatibility and high catalytic activity in a number of reactions.[14] Herein, we report that the cheap cobalt chloride catalyzes efficient α-methoxymethylation as well as α-aminomethylation of ketones with methanol as the sole C1 source (Scheme 1b).

We commenced the study of α-methoxymethylation of ketones with methanol using propiophenone (**1a**) as a model substrate to optimize the reaction conditions, and the results are shown in Table 1. Initially, oxidants were screened with 10 mol % of $CoCl_2·6H_2O$ as the possible catalyst in the presence of Cs_2CO_3 (entries 1, 3, and 4). These experiments revealed that the oxidant plays a crucial role in determining which product is formed preferentially. Different experiments with dioxygen and hydrogen peroxide led to the methylene-bridged product **2a** and methoxymethylation product **3a** in low yields, whereas *tert*-butyl hydroperoxide (TBHP) gave the desired **3a**

Scheme 1. α-C(sp^3)−H Methoxymethylation and Aminomethylation of Ketones with Methanol

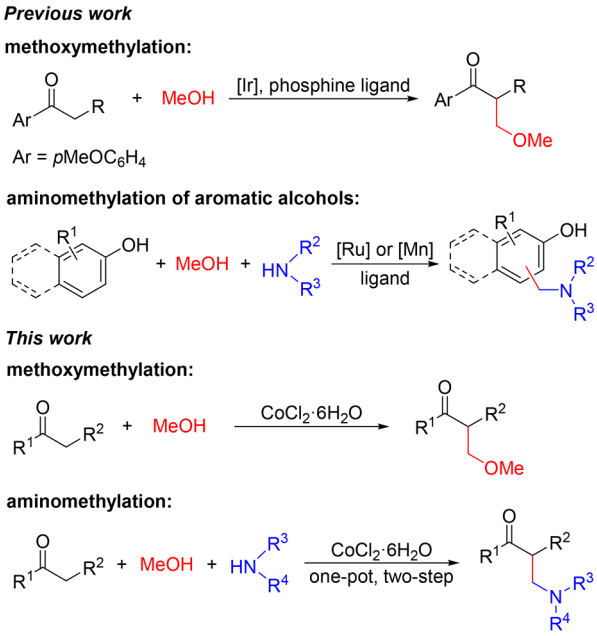


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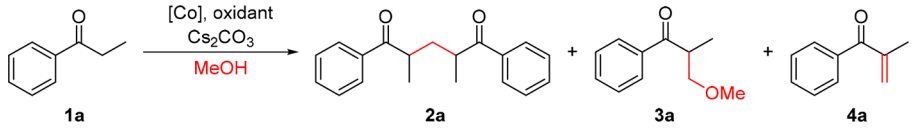
Table 1. Optimization of the Reaction Conditions for α-Methoxymethylation of Ketone with Methanol[a]



1a 2a 3a 4a

					yield[b] (%)		
entry	catalyst (mol %)	oxidant	temp (°C)	time (h)	2a	3a	4a
1	$CoCl_2·6H_2O$ (10)	O_2	65	40	29	5	0
2	$CoCl_2·6H_2O$ (10)	N_2	65	22	2	2	0
3	$CoCl_2·6H_2O$ (10)	H_2O_2 (1.5 equiv)	65	22	11	3	0
4	$CoCl_2·6H_2O$ (10)	TBHP	65	1	0	86	12
5	$CoSO_4·7H_2O$ (10)	TBHP	65	1	0	86	13
6	$Co(OAc)_2$ (10)	TBHP	65	1	0	80	11
7	$CoCl_2·6H_2O$ (10)	TBHP	25	1	0	0	0
8	$CoCl_2·6H_2O$ (10)	TBHP	45	4	0	66	6
9	$CoCl_2·6H_2O$ (10)	TBHP	120[c]	1	0	79	14
10	$CoCl_2·6H_2O$ (10)	TBHP (20 mol %)	65	1	0	23	3
11	$CoCl_2·6H_2O$ (5)	TBHP	65	1	0	86	12
12	$CoCl_2·6H_2O$ (1)	TBHP	65	1	0	86	13
13[d]		TBHP	65	24	0	0	0
14[d]	$CoCl_2·6H_2O$ (1)		65	24	0	0	0
15[e]	$CoCl_2·6H_2O$ (1)	TBHP	65	1	0	5	0
16[f]	$CoCl_2·6H_2O$ (1)	TBHP	65	1	0	75	10
17[g]	$CoCl_2·6H_2O$ (1)	TBHP	65	1	0	49	11
18[h]	$CoCl_2·6H_2O$ (1)	TBHP	65	1	0	0	0

[a]General conditions: **1a** (0.5 mmol), Cs_2CO_3 (1 mmol, 2 equiv), TBHP (0.75 mmol, 1.5 equiv, unless otherwise mentioned), MeOH (3 mL); [b]NMR yield (CH_2Br_2 as internal standard); [c]Performed in a sealed tube; [d]Degassed MeOH was used; [e]Cs_2CO_3 (20 mol %); [f]Cs_2CO_3 (1 equiv); [g]K_2CO_3 (2 equiv) instead of Cs_2CO_3; [h]NaOAc (2 equiv) instead of Cs_2CO_3.

in 86% yield accompanied with a small amount of enone **4a**. Similar results were obtained with other cheap and commercially available cobalt salts, e.g., $CoSO_4·7H_2O$ and $Co(OAc)_2$ (entries 5 and 6). Further investigation indicates that a relatively high temperature and adequate TBHP are required to afford **3a** in high yield (entries 7−10). To our delight, reducing the catalyst loading to even 1 mol % also afforded **3a** in a satisfying yield (entry 12), highlighting the attractive catalytic activity of cobalt salts. Control experiments showed that both cobalt and TBHP are necessary under the conditions employed (entries 13 and 14). Varying the amount of base indicates that sufficient Cs_2CO_3 is needed for high yield of **3a** (entries 15 and 16). When other bases were used in place of Cs_2CO_3, K_2CO_3 gave a low yield and NaOAc did not react at all (entries 17 and 18).

Next, in using methanol as the C1 source, the substrate scope of the cobalt-catalyzed α-methoxymethylation of ketones was evaluated under the optimum reaction conditions (Scheme 2). The propiophenone derivatives with either electron-donating or electron-withdrawing substituents on their phenyl ring were smoothly converted to the desired products in high to excellent yields (**3a−m**). Except for trifluoromethyl (**3h**), the electronic effect of the substituents on the benzene ring only slightly affected the results, albeit without a clear trend. 1-(4-Hydroxyphenyl)propan-1-one with a hydroxyl group was also tested, but no reaction occurred at all. Notably, the heteroaryl thiophene propanone was viable and provided the corresponding α-methoxymethylated product **3n** in good yield. Furthermore, a series of ketones with longer alkyl chains (R^2 = Et, Pr, phenethyl) were also well-tolerated and afforded the desired products (**3o−r**, **3t**) in moderate to high yields. An exception is seen in 1,2-diphenylethan-1-one, which gave the methoxymethylated product **3s** in low yield, probably due to the steric hindrance of the α-phenyl unit and the lower nucleophilicity of the corresponding enolate. It is worth mentioning that while the ketones in which the R^2 is a chloromethyl group were methoxymethylated successfully, the chlorine atom was also substituted by a methoxy group (**3u**, **3v**).

To demonstrate the synthetic utility of this methoxymethylation reaction, a gram-scale experiment of **1a** was performed (Scheme 3). The reaction proceeded smoothly in the presence of only 0.3 mol % of $CoCl_2·6H_2O$, providing the methoxymethylated product **3a** in 75% yield.

In the course of optimization of the reaction conditions, we observed that the enone and methoxymethylated products coexisted in an approximately constant ratio (Table 1, entries 4−6, 11, and 12). Thus, we speculated that there might be an equilibrium between them. To confirm this, two experiments were carried out, one starting from enone **4a** and the other from methoxymethylated product **3a**, in CD_3OD in a NMR tube. As shown in Scheme 4, dissolving either **3a** or **4a** in CD_3OD in the presence of Cs_2CO_3 led to a mixture of both, with **3a**/**4a** = 7:1 in both cases (see the Supporting Information). This result is almost identical to the observation made under the reaction conditions given in Table 1 and supports the notion that the enone and methoxymethylated product are in equilibrium. We therefore surmised that this reversibility could be used to develop a one-pot methylenation/aza-Michael addition sequence to achieve an overall aminomethylation of ketones.

Subsequently, the aminomethylation of ketones was investigated in a one-pot two-step fashion, where the enone and methoxy adduct would be formed first but not isolated;

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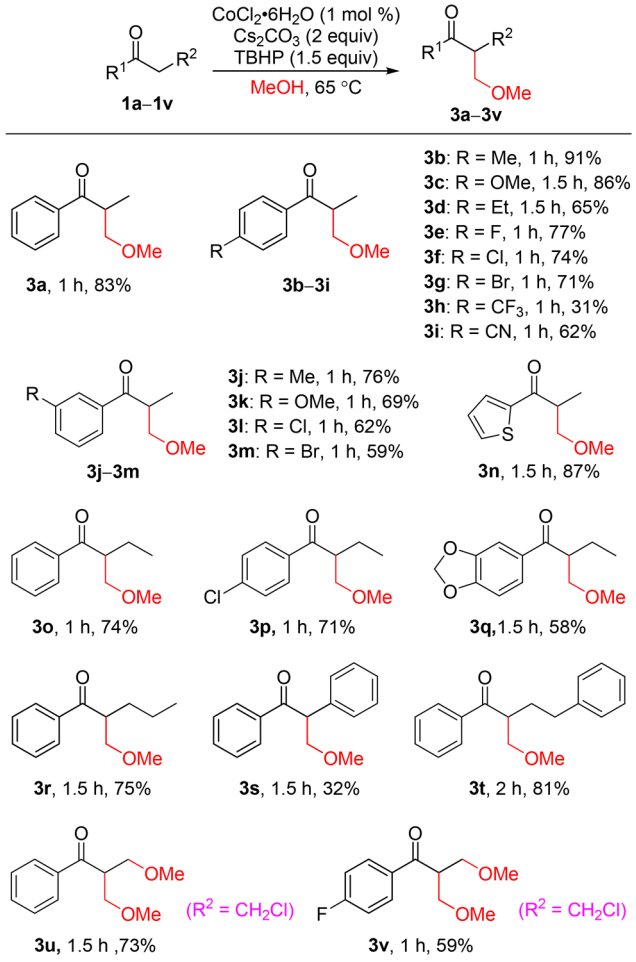
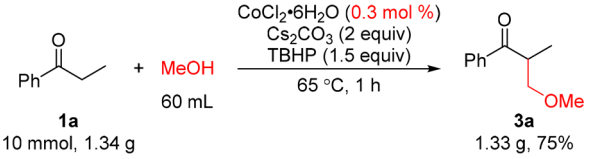
Scheme 2. Scope of α-Methoxymethylation of Ketones with Methanol[a]

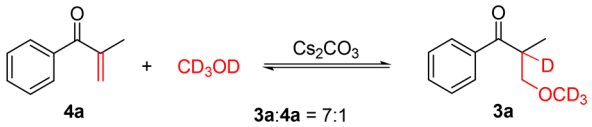


[a]Reaction conditions: **1** (0.5 mmol), $CoCl_2·6H_2O$ (0.005 mmol), Cs_2CO_3 (1 mmol, 2 equiv), TBHP (0.75 mmol, 1.5 equiv), MeOH (3 mL). Isolated yields are given.

Scheme 3. Gram-Scale Methoxymethylation of Ketone 1a

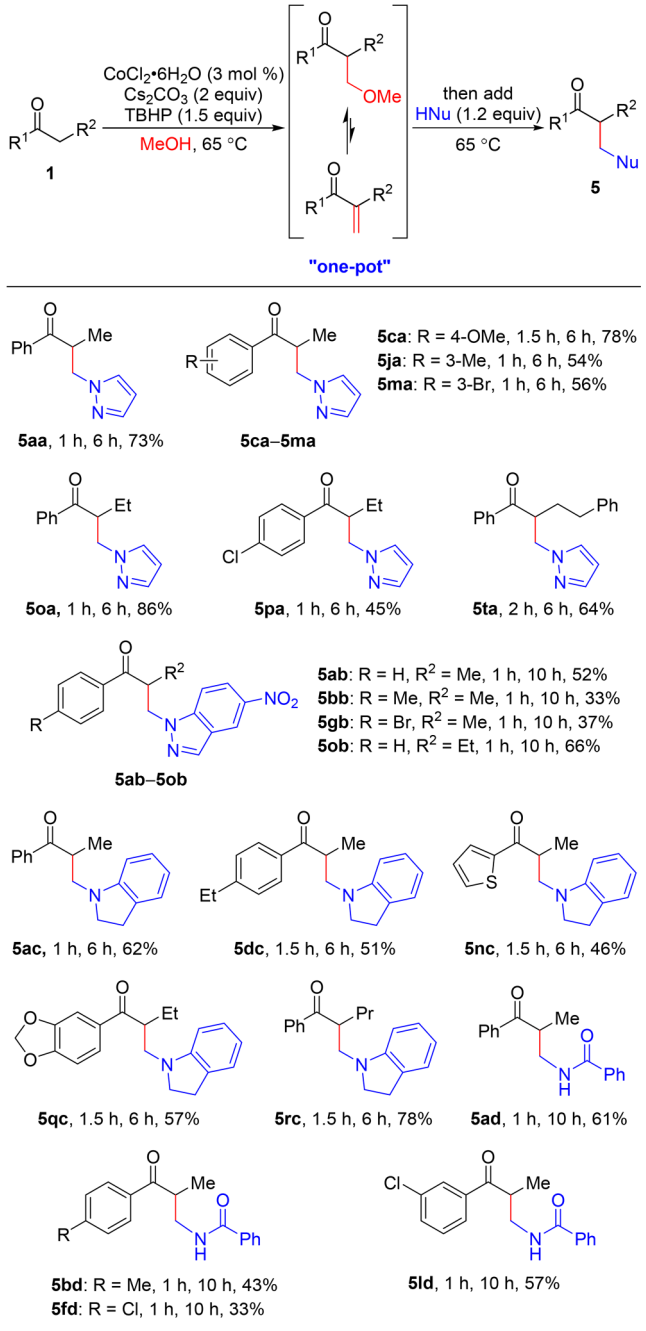


Scheme 4. Experiment Showing Equilibrium between Enone 4a and Methoxymethylated Product 3a



instead, it would be reacted in situ with an external N-nucleophile (Scheme 5). Considering the diverse bioactivities of N-heterocycles and important applications of aromatic amides, pyrazole, 5-nitro-1*H*-indazole, indoline, and benzamide were tested. As expected, these compounds were viable in this one-pot, two-step aminomethylation reaction. In particular, pyrazole gave the corresponding aminomethylation products **5aa**−**ta** in moderate to high yields, while 5-nitro-

Scheme 5. One-Pot α-Aminomethylation of Ketones with Methanol and N-Nucleophiles[a]



[a]Reaction conditions: **1** (0.5 mmol), $CoCl_2·6H_2O$ (0.005 mmol), Cs_2CO_3 (1 mmol, 2 equiv), TBHP (0.75 mmol, 1.5 equiv), MeOH (3 mL). Isolated yields The times shown refer to the reaction time for the first and second steps, respectively.

1*H*-indazole, indoline, and benzamide generally produced the target products **5ab**−**ld** with relatively low yields. In comparison with the aza-Michael reactions using isolated enones, the yields appear to be lower here.[15]

To gain an understanding of the aminomethylation reaction, several reactions starting from the methoxymethylated product **3a** were performed in the absence of cobalt and TBHP (Scheme 6). As can be seen, **3a** reacted well with pyrazole in the presence of Cs_2CO_3, affording the aminomethylated product **5aa** in 86% yield, which is higher than that obtained

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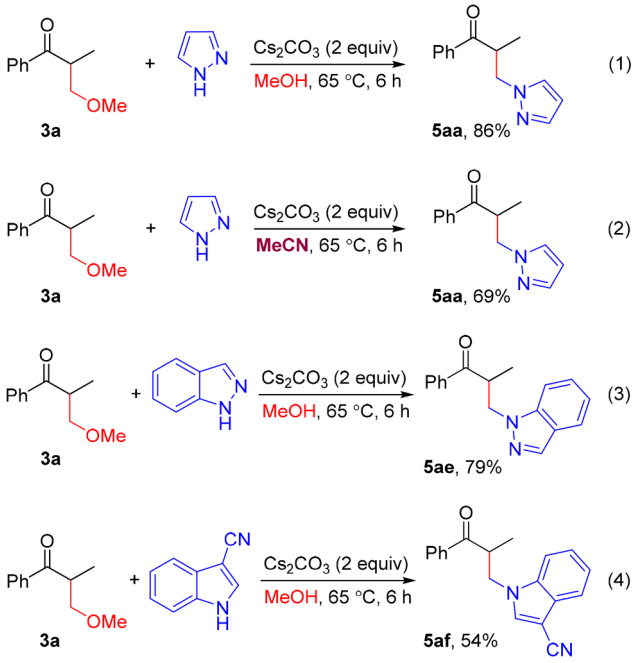
Scheme 6. Effects of Reagents on the α-Aminomethylation of Ketones

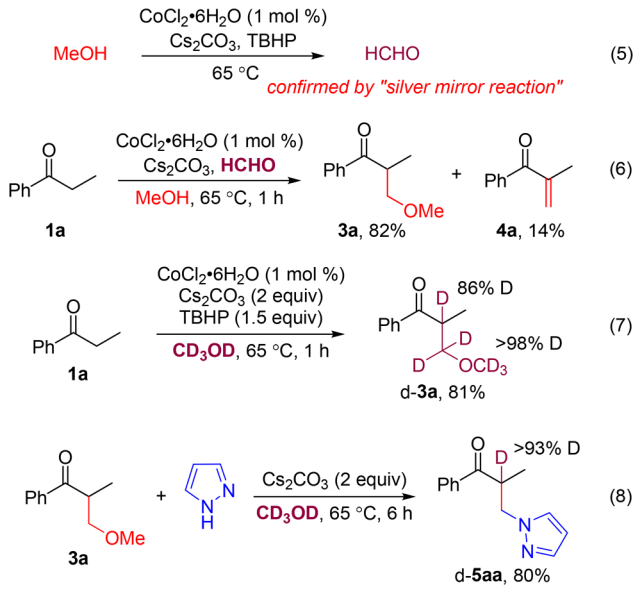


in the one-pot aminomethylation. This implies that cobalt only plays a role in the first step of the cascade reaction and TBHP has a negative effect on the second step of the reaction (Scheme 6, eq 1). In addition, **5aa** was also obtained with acceptable yield in acetonitrile, showing that methanol is not irreplaceable for the second step (Scheme 6, eq 2). Starting with **3a**, indazole and 3-cyanoindole, which resulted in a complex mixture in the one-pot aminomethylation, the corresponding products **5ae** and **5af** were obtained in 79% and 54% yields, respectively (Scheme 6, eqs 3 and 4). This further indicates the negative effect of TBHP on the second step of the reaction, accounting for the unsatisfactory yields gained in the one-pot aminomethylation. On the other hand, this finding provides a promising protocol for converting α-methoxymethyl ketones into the α-aminomethyl variants.

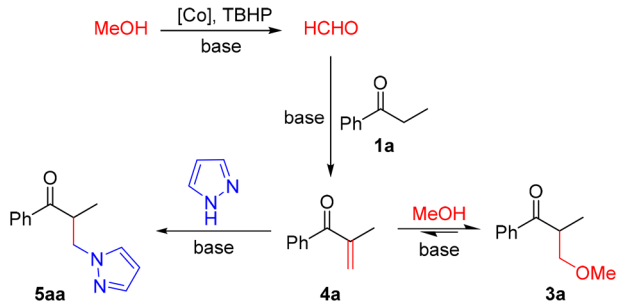
To probe further the mechanism of the reaction, a series of control experiments were conducted (Scheme 7). First, the in situ conversion of methanol to formaldehyde under the reaction conditions was confirmed by a silver mirror reaction (Scheme 7, eq 5). Second, formaldehyde, in the absence of TBHP, gave a similar result in terms of yield and ratio of **3a** and **4a** (Scheme 7, eq 6). These results clearly indicate that methanol is oxidized to formaldehyde, which as a key intermediate is involved in the subsequent methoxymethylation. Carrying out the reaction of **1a** in deuterated methanol led to the corresponding deuterated product d-**3a**, revealing that methanol is indeed involved in the methoxymethylation (Scheme 7, eq 7). Reacting **3a** with pyrazole in deuterated methanol afforded d-**5aa** (Scheme 7, eq 8), which is in line with the equilibrium shown in Scheme 4 and the α hydrogen in **5** being acidic.

Although the precise mechanism is not yet clear, a possible reaction pathway is proposed based on the observations above (Scheme 8). First, methanol is oxidized to formaldehyde in the presence of the cobalt catalyst and TBHP. Then the resulting formaldehyde reacts with ketone **1a** via its base-promoted enol form to produce the equilibrating enone **4a** and methoxymethylated product **3a**. In the presence of an external N-nucleophile, the mixture of **4a** and **3a** is converted into the aminomethylated product **5aa** via the aza-Michael reaction of **4a**. We do not yet know the mechanistic details of how the cobalt catalyzes the formation of formaldehye. However, Co(II) compounds are known to promote the oxidation of various compounds including alcohols with TBHP via radical pathways.[16]

Scheme 7. Further Experiments To Probe the Reaction Mechanism



Scheme 8. Proposed Reaction Pathway



In summary, using methanol as a sustainable C1 building block, we have developed a cobalt-catalyzed strategy for α-methoxymethylation and α-aminomethylation of ketones. With 1 mol % of cheap $CoCl_2 \cdot 6H_2O$ as catalyst, a variety of ketones are converted to the corresponding methoxymethylated and aminomethylated products with good yields in general. Formaldehyde, generated in situ from methanol, is a key intermediate in the transformations. The methoxymethylated product appears to be in a fast equilibrium with its enone form, enabling the one-pot aminomethylation of ketones with external N-nucleophiles. In addition, α-methoxymethyl ketones are easily converted into α-aminomethyl ketones in the presence of a base.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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